UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,567	09/04/2003	Futoshi Okada	Furuya Case 1407	6434

23474 7590 10/13/2005

FLYNN THIEL BOUTELL & TANIS, P.C.
2026 RAMBLING ROAD
KALAMAZOO, MI 49008-1631

EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/655,567	OKADA ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

Response to Arguments

Applicants' arguments, see Appeal Brief, filed on August 9, 2005, with respect to the rejection(s) of claim(s) 16-23 under final rejection have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. In view of the new ground of rejection set forth below, however, the finality of the previous Office action is hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting malignant tumor progression in mice and for inhibiting tumor metastasis in mice, does not reasonably provide enablement for inhibiting malignant tumor progression in any subject or for inhibiting tumor metastasis in any subject, in particular in humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. As a result, the scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an

artisan of ordinary skill in the art to determine that gliadin-coated SOD can inhibit malignant tumor progression tumor metastasis in any subject, most importantly in humans.

The state of the art in curing cancer in humans is unpredictable, as stated by Dr. Richard Klausner (Gorman et al., "The hope and the hype," Time 151(19):40-44, 1998, see also enclosed HTML copy, reference pages 1-9). "We have cured mice of cancer for decades - and it simply didn't work in people" (p. 1, 5th paragraph). Further, the state of the art with angiogenesis inhibitors is unpredictable, as stated in the same article, "Nor will angiogenesis inhibitors work equally well against all cancers" (p. 3).

With regards to tumors implanted under the skin in mouse models, "[m]ice distort or exaggerate what you see in humans," according to Robert Kerbel, because they "grow much more rapidly than deep-seated human tumors." (see p. 8, last two paragraphs). Further, it is stated that, "rodents are better predictors of human reaction to cardiovascular or anti-inflammatory agents than to cancer or diseases of the central nervous system" (see p. 8, last paragraph). The article states that J. Michael Bishop, "...is breeding mice to provide better models for studying leukemia..." and that the similarity between mouse and man, "is still a legitimate issue" (see p. 8, next to last paragraph).

Additionally, with regard to *in vivo* models, Gura states, "Pharmaceutical companies often test drug candidates in animals carrying transplanted human tumors, a model called a xenograft. But not only have very few of the drugs that showed anticancer activity in xenografts made it into the clinic, a recent study...suggests that the

xenograft model missed effective drugs. The animals apparently do not handle the drugs exactly the way the human body does," (Gura, "Systems for identifying new drugs are often faulty," Science 278:1041-1042, 1997) and with regards to xenograft models, "tumors don't behave like naturally occurring tumors in humans - they don't spread to other tissues, for example. Thus, drugs tested in the xenografts appeared effective but worked poorly in humans." (see p. 1041, 2^{d} and 3^{d} paragraphs). Further it is stated that they, "had basically discovered compounds that were good mouse drugs rather than good human drugs" (see p. 1041, 7th paragraph). Alan Oliff states in Gura that, "[t]he fundamental problem in drug discover for cancer is that the model systems are not predictive at all." (see p. 1041, 2^{d} paragraph).

Because the model systems are highly unpredictable for treating cancer and the problem of identifying effective compounds in one animal when they are tested in another animal remains largely unsolved, methods for treating, curing, or preventing malignant tumors, as well as for identifying and preparing an effective amount (dose) of the compositions for treating, curing, or preventing malignant tumors is highly unpredictable.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed

invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary (immense, because Applicants claim a method of inhibiting malignant tumor progression and a method of inhibiting tumor metastasis in any subject when the have provided experimental data from a mouse model only), (2) the amount or direction or guidance presented (no guidance is presented for inhibiting tumor progression or tumor metastasis in animals other than mice, and, in mice, only one tumor cell line was tested- QR-32 cells- and only one gliadin-coated SOD was tested, SOD from melon, the commercial product Oxykine®), (3) the presence or absence of working examples (a working example is present for inhibiting the growth and spread of tumors caused by QR-32 cells on sponges implanted into mice by treating the mice with Oxykine®), (4) the nature of the invention (a method of inhibiting the progression and the metastasis of tumor cells comprising administering gliadin-coated SOD to subjects),(5) the state of the prior art (gliadin-coated, melon SOD is known, see Postaire et al., discussed below; SOD has been shown to inhibit tumor metastasis in mice, see van Rossen et al. and Takenaga et al., discussed below; and SOD has been shown to inhibit tumor growth in mice, see Das et al., discussed below), (6) the relative skill of those in the art (very high, that of highly trained research scientist), (7) the predictability

or unpredictability of the art (see below), and (8) the breadth of the claims (broad, as discussed above).

To demonstrate that gliadin-coated SOD can inhibit tumor progression and tumor metastasis in humans, or in animals other than mice, many experiments would have to be conducted. In these experiments, gliadin-coated SOD, at a wide range of doses and dosing regimens (administering the drug once a day, administering the drug at different numbers of times per day) would have to be tested. The drug would have to be given to a wide range of subjects with malignant tumors, e.g., humans, dogs, cows, horses, pigs, chickens, etc. The results of the experiments would have to show that many different doses of gliadin-coated SOD, in many different dosing regimens, inhibit the progression and metastasis of malignant tumors in many different animals.

Such experiments and data are missing from the specification. A great deal of guidance is needed to establish that gliadin-coated SOD can inhibit tumor progression and metastasis in any subject, because the invention is claimed as such, while the specification presents data from one mouse model only. Even if tumor progression or tumor metastasis is shown to be inhibited in one type of animal other than mice, e.g., dogs, without a very large amount of data, such a result could not be expected with a different type of animal, e.g., humans.

Regarding predictability, because the specification does not provide guidance for treating tumors in animals other than mice, it cannot be predicted that tumor progression or metastasis can be inhibited in any subject by administering gliadin-coated SOD. Accordingly, the claims fail to satisfy the enablement requirement.

Claim Rejections - 35 USC § 103

Claims 16-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ginoux (U.S. 5,616,323) in view of Postaire et al. (U.S. 6,045,809), Takenaga et al. ("Effect of lecithinized superoxide dismutase (PC-SOD) on experimental pulmonary metastasis in mice," Free Radic Biol Med 26(9-10):1117-1125, 1999), van Rossen et al. ("Scavenging of reactive oxygen species leads to diminished peritoneal tumor recurrence," J Cancer Res 60:5625-5629, 2000) and Das et al. ("Inhibition of tumor growth and inflammation by consumption of tea," Phytother Res 16 (Suppl 1):S40-44, March 26, 2002).

The teachings of Ginoux and Postaire et al. were discussed in previous Office actions. To recap briefly, Ginoux discloses administering SOD-containing extracts from melon to treat cancer (see column 1, lines 6-10 and 59-65, column 2, lines 21-24, and column 5, lines 13-29). Postaire et al. disclose a composition comprising superoxide dismutase (SOD) and gliadin, which stabilizes this enzyme at acidic pH and provides a controlled release formulation that has improved bioavailability (absorption) compared to prior compositions (see column 3, lines 1-11). The plasma half-lives of uncoated SODs are very short (see col. 1, lines 37-39). It would be obvious to one of ordinary skill in the art at the time that the invention was made to formulate the SOD-containing melon extract of Ginoux as a gliadin-coated composition according to Postaire because Postaire discloses that the gliadin-coated composition is more acid-stable, for oral administration, longer acting, and absorbed by a subject following oral administration.

Neither of these references discloses administering SOD to inhibit malignant tumor progression or tumor metastasis.

van Rossen et al. disclose that intraperitoneal administration of SOD to mice inhibits the metastasis of tumors to various organs in the abdominal cavity (see Abstract; p. 5625, 3^{d} paragraph; p. 5626, last full paragraph; p. 5627, last full paragraph; and p. 5628, Table 2). Das et al. disclose that, when black or green tea extract is administered to mice intragastrically, serum levels of SOD increase, and this increased SOD activity inhibits the progression of a tumor (see p. S40, Abstract and last two paragraphs; p. S41, paragraph entitled Tumour Growth; p. S42, Fig. 2; and p. S43, 2^{d} and 3^{d} full paragraphs). Takenaga et al. disclose that, when lecithinized SOD is administered intravenously to mice, the metastasis of pulmonary tumors is inhibited by about 50% (see Abstract, p. 1119 and p. 1120, Fig. 1).

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to administer the gliadin-SOD composition of Postaire et al. to inhibit the metastasis of tumors in mice, such as lung tumors or peritoneal cavity tumors, because Postaire et al. teach that gliadin coating is a superior way of preparing SOD, or an SOD-containing extract, for oral administration. Takenaga et al. teach that SOD inhibits the metastasis of lung tumors in mice, and van Rossen teaches that SOD inhibits the metastasis of tumors to other regions of the body in mice, i.e., the abdominal organs. Das et al. teach that SOD inhibits tumor growth in mice. It would have been obvious to one of ordinary skill in the art at the time that the invention was made to administer gliadin-coated SOD to mice to inhibit tumor progression or metastasis

because Das et al. teach that SOD inhibits tumor progression in mice, while van Rossen et al. and Takenaga et al. teach that SOD inhibits tumor metastasis in mice. Although Takenaga et al. disclose partial, not total, inhibition of lung tumor metastasis, in their treatment method, the SOD preparation was administered to the mice before the tumor cells were administered (see p. 1118, top of the right col.). Treatment of the mice or of the tumors with the SOD preparation for a period of time following placing the tumor cells in the mice may have produced a better result. Additionally, the mice were treated with lecithinized SOD (phosphatidylcholine-conjugated), rather than gliadin-coated SOD, which, as noted by Postaire et al. has improved properties of stability and absorption.

In view of the foregoing, a holding of obviousness is required.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner, Art Unit 1653

rk/2005-10-05

ROBERT A. WAX
PRIMARY EXAMINER